



Review article

Regulation & registration of drugs and biologics in Brazil

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ABSTRACT

Registration of medicinal products is a challenging task in various countries as the regulatory requirements differ from country to country around the world. Like in regulated countries medicinal products regulation is a difficult piece of work in Semi-regulated countries as they are not coordinated. Being the sixth most populous country, Brazil gives a great opportunity for the bio/pharmaceutical market. Superior health maintenance, high quality, and modern medicines are being demanded by Brazilians which gives a huge opportunity for overseas investment. Medicinal products registration is a lengthy process in Brazil. Obtaining access to the marketing of drugs and biologics from the Brazilian Regulatory Authority is not an easy business for bio/pharmaceutical companies. One of the most difficult tasks facing regulatory agencies is ensuring that medications are manufactured in accordance with the country's regulatory requirements. This Review article's primary objective is to explain how pharmaceuticals and biologics are regulated and registered in Brazil.

Keywords: Brazil, ANVISA, Drugs, Biologics, Regulation

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INTRODUCTION

Brazil is the largest in terms of area and most populated country with around 200 million residents in South America. Being the 8th largest pharmaceutical market in world, Brazil is currently the vital target for big investments and marvellous outlook for large pharmaceutical markets^[1]. Biopharmaceutical market in Brazil has showed more advanced and striking changes since 2000, with the enhancement in the conduct of domestic trade, consumer demand and productive capacity^[2]. Because of Brazil's emerging industry, bio/pharmaceutical companies from all over the world are eager to invest in this vast market. Nonetheless, when dealing with Brazil's convoluted regulatory process, this prospect poses a significant hurdle.

Figure 1: Brazil's Location**Regulatory agency - ANVISA**

The Brazilian Health Surveillance Agency, often known as ANVISA, abbreviated from Portuguese Agencia Nacional de Vigilance Sanitaria^[3]. ANVISA is the Brazilian Regulatory Authority that is liable for approval and surveillance of foods, medicines, cosmetics, tobacco, public health, medical devices and maintaining cleanliness of ports, airports^{[4][5]}. ANVISA was established in 1999 via the Law 9.782/1999 and is associated with Ministry of Health. The main objective of ANVISA is to safeguard and improve the health of people by forbidding the manufacturing and use of products and facilities that are harmful to public^[6]. ANVISA is in charge of developing regulations for clinical trial and registering drugs and biologics. It is governed by five board members and is described as financially and administratively independent agency. In November 2016, ANVISA has become a new regulatory member of the International Council on Harmonisation (ICH) & the organisation has been striving diligently to prioritise & upgrade its resolution to familiarize ICH recommendations.

There are geographical differences and parallels between the CTD format used in the ICH countries members and the Brazilian registration. The Brazilian dossier consists of two primary sections:

Administrative Information: Includes all administrative data, and also certain necessities for imported products.

Technical Section: Includes Technical reports, comprising

of quality, nonclinical, and clinical information, identical to the CTD Modules 2, 3, 4, & 5.

Organizations that are a part of Authorisation procedure in Brazil

Three distinct agencies in Brazil are in charge for evaluating and authorizing regulatory documentation to start a clinical study: CONEP (Central), CEP (Local Committee), and ANVISA. The CONEP and ANVISA processes run simultaneously. National Committee of Ethics in Research (CONEP) is the Central Ethics Committee, which is affiliated to the Ministry of Health and is in charge of reviewing and approving the ethical elements of a clinical trials in Brazil^[3].

Definitions and Regulations of drugs in Brazil

New Drug

These are innovator drug products whose safety, efficacy, quality are demonstrated with the help of non-clinical and clinical studies before registration in ANVISA. A novel molecular entity, a novel or modified structure, a new indication, a new dosage form, a new dose administration method, a new combination, or a new therapeutic role can all be found in innovator medicinal formulations. Innovator drugs are the products against which generic and similar drugs are evaluated.

The marketing authorization of innovator drugs requirements are given in:

- The registration of medicines, drugs, pharmaceutical goods is governed by Law No. 6,360/1976. This law contains the majority of the regulations governing pharmaceutical items in Brazil.
- Resolution No. 136/2003 governs the marketing clearance of novel medications in Brazil.

There are a few prerequisites that must be met in order to register a novel drug, encompassing the "product be recognised as safe and effective"& that comprehensive data be submitted (Article 16, Law No. 6,360/1976). To acquire marketing clearance, a technical report, as well as reports from pre-clinical and clinical trials, must be submitted in accordance with the specific rules outlined in Resolution No. 136/2003. Brazilian regulators, on the other hand, are still awarding marketing approvals for novel pharmaceuticals to domestic companies that have yet to undertake a clinical trial^{[7][8]}.

Generic Drug

A medicine that is bioequivalent to the reference drug and has the same active component, dosage form, route of administration, strength, and therapeutic application as the innovator medication.

These can be interchangeable with innovator drug and are produced only after expiration of patent and exclusivity rights, whose safety, efficacy, quality should be demonstrated, and designated by CBD (Common Brazilian Denomination) or failing this, by the CID (Common International Denomination)^{[9][10]}.

Ministry of Health, approved the Generic Drug Act in 1999 in Brazil under Law n. 9.787/1999, and may be marketed if pharmaceutically equivalent to the reference product & produced to ANVISA quality standards^[11]. Generic drugs normally have a price 65% lesser than the patent drugs or innovator drugs.

Similar medicines

These are branded generics which are said to have same active ingredients, dosage form, strength, indication, and dose as that of innovator drugs. These drugs already existed from a long time before introduction of generics in 1999^[12]. Marketing approval requirements for these products are published under Resolution No. 1/1994.

Studies on pharmacokinetics and pharmacological equivalence have been established as conditions for authorisation of similar products by Resolution RDC No. 133 of May 29, 2003. This resolution also allowed similar drugs with different pharmacokinetic features, such as area under the curve (AUC) and Cmax, to be compared to their reference product. In such cases, additional efficacy and safety studies are not required, but the product must be registered with altered dose or doses requirements.

RDC No. 134/2003 states that the similar drugs which have previously been accepted should adhere to Resolution No. 133/2003's rules, if not then convert their registration to innovator drugs by submission of clinical studies.

Resolution No. 17/2007 annulled Resolution No. 133/2003 & mandated that similar medications undergo the same in vitro study standards as generic drugs, including statistical analysis. Resolution No. 17/2007, on the other hand, does not stipulate that these pharmaceuticals must be bioequivalent to their reference products, and that similar medications are not interchangeable with their reference medicines^[7]. Since 2014, all similar medications have demonstrated therapeutic equivalence, allowing them to be substituted for reference drugs^[12].

In 2014, RDC No.60/2014 was published for registration of drugs (Innovator, generic, similar drugs) in Brazil^[13]. Current Regulation for Marketing Authorisation of drugs (Innovator, generic, similar drugs) in Brazil is Resolution RDC 200/2017^[14].

Registration of New Drug

Pre-Registration (Protocol for clinical study)

RDC No.39/2008 resolution accredits the regulations for performing clinical trials. This resolution defines clinical trials, as well as the documentation required for clinical studies and drug importation. ANVISA controls the performing& monitoring of clinical trials of Clinical Research Organizations^[15]. The results of clinical studies are need to be submitted.

Registration Dossier Requirements

Administrative Documents

- Registration fee payment proof

- License for Manufacturing
- Free Sale Certificate/Export Certificate
- Drug registration and marketing documentary proof in the country of origin
- Information regarding the registration of drug around the world
- Pharmacovigilance data
- CoPP(Certificate of Pharmaceutical Product)
- GMP Certificate issued by ANVISA
- GMP Certificate provided by Regulatory Authority in native land
- Photocopy of GMP certificate in country of origin for imported products
- Labelling in Portuguese
- Justification for product registration
- Local representative sanitary license
- Samples of finished product

Technical Documents

Following information regarding API should be included

- API Nomenclature, General properties, Structure Elucidation
- API Manufacturer Name, manufacturing site
- Stability testing
- Stability data
- Manufacturing Formula
- Description of Manufacturing process
- Master formula, BMR
- Critical steps and process
- Process Validation
- Formulation & Development
- Batch Analysis
- COA (Certificate of Analysis)

Excipients

- Permitted excipients should be used
- Specification of Microbial limit
- Excipients COA
- TSE/BSE certificates

Finished product

- Formulation development description
- Description of composition
- FP stability studies
- Details of method of Analysis
- In accordance to pharmacopoeia specifications if not, then ought to be in accordance with ICH Q6A guidelines

Stability data

- Physical, chemical, biological, and microbiological

properties, as well as preservative content and functionality tests, should all be included in stability testing.

- Product's Shelf life
- Storage conditions
- Because Brazil is in climatic zone IVb, long term stability studies ought to be undertaken at $30^{\circ}\text{C} \pm 2^{\circ}\text{C}$ & $75\% \pm 5\%$ RH for 12 months, while accelerated stability studies need to be conducted at $40^{\circ}\text{C} \pm 2^{\circ}\text{C}$ & $75\% \pm 5\%$ RH for 6 months.
- If stability batch fails in above cases, an examination at $30^{\circ}\text{C} \pm 2^{\circ}\text{C}$ & $65\% \pm 5\%$ RH can be conducted.

Packaging Material

- The packaging material should be acceptable for storage and transit while also ensuring that the medicine is not harmed.
- Detailed requirements and methods of analysis are required for primary and secondary packaging materials.

Non-clinical study reports

- Pharmacological, Toxicological data
- Pharmacokinetic data

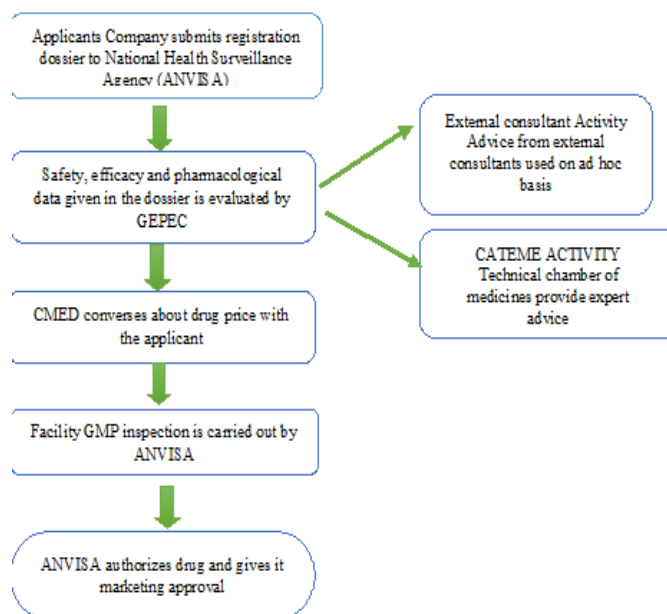
Clinical Study Reports

- Pharmacokinetic and pharmacodynamic research in humans
- Efficacy and Safety studies
- After-sales information in case

Time & Fees for Registration in Brazil

Time and fee required for registration of drug in Brazil depends on the type of drug. It takes 12-14 months for Innovators, 6-8 months for Generics & 8-12 months for Similar Drug. Fee of about 2700 USD-27000 USD, 2000 USD & 7000 USD for Innovators, Generics& Similar Drugs respectively^{[16][17]}.

Registration Dossier Review Process



GEPEC: Office for New drugs, Research and clinical trials

CMED: Chamber of Drug Market Regulation^[18]

- Registration of a product is effective for 5 years and it's possible to renew on a regular basis for the same time^[15].

GMP Inspection by ANVISA Requirements for GMP Inspection

- Petition form
- GMP certificate from the nation of origin's regulatory organisation
- Plant master file
- Review of the product

Timelines for inspection

Manufacturing site inspection by ANVISA takes place approximately 6 months after filing the request for inspection.

If all the requirements are in accordance with regulations of Brazil, then ANVISA may grant GMP certificate to imported medicines manufacturers within 45 to 60 days after inspection^[18]. GMP certificate is essential for Marketing Authorization. In Brazil, GMP certificate is valid for two years^[19].

Local Testing Requirements

Finished products Quality control tests should be done by importers in Brazil and it should comply with regulations set down by ANVISA.

If >8 shipments of each drug are imported every year then samples of two batches/year are to be examined

If ≤ 8 shipments of each drug are imported /year, then samples from two batches are to be examined every two years^[18].

Drug Labelling

The label should include Name of the product, Ingredients with their quantity, Dosage form, Dose, Manufactured date, Expiry date, Batch number, Manufacturer information, Storage conditions, Side effects, Directions on how to use the product, Warning Phrases like “ALL MEDICATION MUST BE KEPT OUT OF CHILDREN'S ACCOUNT” should be written in capital letter.

Package inserts gives details to patient, physicians, indications, contra-indications, precautions.

Labelling on the package should be in Portuguese^{[16][20]}.

Post-Registration Measures

“Guide for making post-registration alterations and inclusions in medicines” should be complied for any change in registration.

Conformity and Quality of Registered drug is monitored by analysis of commercialised batches in laboratories, which is a responsibility of ANVISA. If needed, training of technicians to handle these monitoring's may also be requested by ANVISA^[16].

Registration process for generic drugs is similar innovator drugs. But generic drugs are required to submit only Module1, Module3, Module 5 (BE studies). It does not require preclinical, clinical and bioavailability studies^[20].

External consultant Activity Advice from external Consultants used on ad hoc

Brazil's Regulatory Obstacles to Drug Registration

In both the administrative and quality aspects of dossier, there are numerous complex and country-specific criteria for drug product registration in ANVISA. Legalization of the submitted CoPP is required from the Brazilian government. ANVISA shall examine and approve both the API supplier and the API manufacturer's manufacturing facilities.

The applicant must submit samples to ANVISA for pharmaceutical equivalency in order to register a generic medicine. At the Brazil Lab for analysing, a comparative dissolution profile will be done with a Brazilian reference medication in accordance with RDC 31/2010. Analytical method validation and Bioequivalence studies must be undertaken in ANVISA-certified laboratories after passing the tests.

ANVISA allocates drug prices using a correlative characteristic, which states that the cost cannot be more than the cheapest cost of that drug sold in nations like Australia, Canada, and US etc or higher than the price set by the manufacturer in the country where the product was made. If a non-competitive price is fixed, corporations may elect not to commercialise the approved medicine^[16].

Biologics

Definitions

Biologic Products

Biologic products are large complex molecules manufactured or extracted from a biological source that have the capacity to prevent or cure or treat a disease. These are the medicinal products obtained from living system like micro-organism, plant cell, animal cell etc; using biotechnological methods. These can include complex carbohydrates, proteins, nucleic acids or tissue extracts^[21].

Biosimilars

These are the biotherapeutic products that are highly similar to reference biologic product with no clinically meaningful differences in safety, efficacy, quality characteristics or biological activity and are generated by recombinant DNA techniques in live creatures^{[22][23]}. Similarity can be demonstrated with the help of comprehensive comparability exercise^[22]. As they are produced using the different cell lines different manufacturing and purification processes, they are not identical to the reference biologic.

Biosimilars cannot be considered as generics. While generics need illustration of having same active ingredient, dosage, strength and bioequivalence with that of reference product; biosimilars require comparative studies to ensure that the variations with that of the

reference product is minimum without any clinical involvement. Biosimilars are more complex and sensitive unlike generics [24].

Table: 1 Generics vs Biosimilars

Generics	Biosimilars
Consists of same active substance as that of a branded drug	Should be highly similar to reference biologic product
Molecular weight is low	Molecular weight is high
Structure is small and less complex	Structure is large and more complex
Manufacturer has to demonstrate BE studies	Biosimilars must be shown to be very similar to the reference biologic product, with no clinically significant deviations by the manufacturer
These are more stable	Sensitive to changes in physical condition
Manufacturing process is less complex	Manufacturing process is complex, lengthy and expensive
Made by organic or chemical synthesis	Obtained from living systems like micro-organisms, plant cell
Reproducibility is easy to establish	Reproducibility is difficult to establish
Production cost is less	Production is expensive

Biologics in Brazil

ANVISA oversees the registration of biological products and has established rules for biologics licencing. The following are some examples of biological products in Brazil: (1) Antivenom immunoglobulins; (2) vaccinations (3) Blood and blood products; (4) Biomedicines derived from a) biological fluids or animal tissues, b) biotechnological techniques; (5) monoclonal antibodies; (6) medications containing live, attenuated, or dead microorganisms; (7) Probiotics, (8) Allergens.

Regulation of biologics in Brazil

First legislation for biologics was formed in 1994 under Ruling No.107 even though ANVISA was constituted in 1999. ANVISA set down first regulation for biologic products in 2002 under RDC No. 80/2002. This resolution distinguishes biologics products as that include a molecule with recognised biological activity; and those which include a molecule with new biological activity and can have patent protection (new biologic product). Biosimilars (follow on biologics) and new biological drugs have same pathway for registration under this resolution. Details regarding production and quality control of biologics, preclinical and clinical studies are need to be submitted under RDC No. 80/2002.

In 2005, under RDC No. 315/2005, a new registration for biological products was constructed very swiftly, three years after the initial regulation was released. This resolution was more stringent than the former one, requiring details on the production process, transportation chain validation, and clinical trials on the non-inferiority of non-new biological products.

ANVISA revised the regulations for biologic products in 2010, by promulgating Resolution RDC No. 55/2010 and this is the current regulation for biologics in Brazil. This resolution in turn brought new terminology

- New Biologic product: A new biologic product is one that

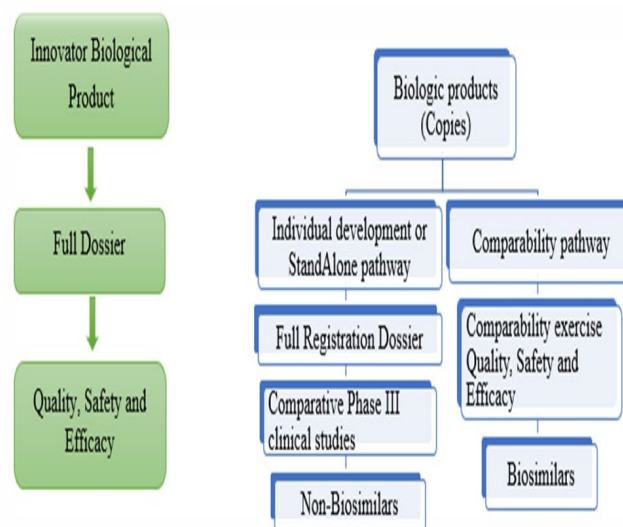
contains a molecule with recognised biological activity but has not yet been registered in Brazil.

- Biologic product: A drug containing a chemical with recognised biological action that has been approved in Brazil.

The main objective of this denomination is to make it apparent that bio-similarity is not a prerequisite for copy biologic product clearance in Brazil [24].

Resolution RDC No. 55/2010 in turn demonstrated novel regulatory approaches for innovator biologic product and copies of biologic products. For copies of biologic product there are two different pathways (i) comparability pathway; (ii) individual development pathway.

Figure 2: Current Regulation on Biological Products(RDC No. 55/2010-Marketing Authorisation of biological product)



Comparability Pathway – Biosimilar Approach

This pathway involves Head to Head comparison of biologic product (copy) with comparator product.

Comparator Product: It is a biological product already approved through ANVISA by filing a complete dossier and that has already been marketed in Brazil. Comparability exercise is carried out with the help of same comparator in all stages.

Quality, Non-clinical, Clinical phase I, II, and III trials information of biologic product (copy) is compared with comparator or reference product. This pathway is suitable for more complex biotherapeutic molecules like monoclonal antibodies. Biologic product registered through this pathway are known as Biosimilars [31].

Individual Development or Standalone Pathway

Biological products (copies) in Brazil can also be approved through individual development route. In this pathway dossier requirements are reduced, the applicant must submit the documents related to the quality, preclinical and phase I&II clinical trials which are not comparative, but results of the phase III clinical trial must be comparative [24][32]. Biotherapeutics with fewer complications, such as pegylated interferon and low molecular weight heparin will likely go

through this pathway resulting in non-biosimilars^[32].

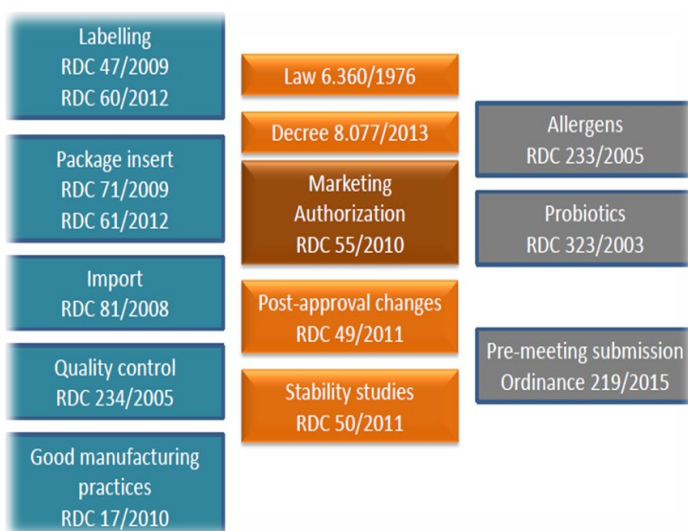
Table 2: Data requirements for registration of biologics in Brazil

Data requirements	Innovator biological products	Biologic products	
		Comparability pathway	Individual development or Stand Alone pathway
Chemistry, manufacturing and controls documentation	Required	Comparative	According to standards
Preclinical studies	Required	Comparative	Requirements may be reduced
Phase I clinical studies	Required	Comparative	When necessary and may not be comparative
Phase II clinical studies	Required	Comparative	When necessary and may not be comparative
Phase III clinical studies	Required	Comparative	Comparative with exceptions
Immunogenicity	Required	Comparative	Required
Same comparator	This doesn't apply	Yes	This doesn't apply
Risk management plan	Required	Required	Required
Extrapolation of indications	This doesn't apply	Possible	Not Possible

Biologic products can be registered through any of these pathways with ANVISA. After registration, price of biologic products will be determined by the Medication Chamber (CMED) and then they can be marketed in Brazil^[24].

According to Brazilian legislations, there is no time limit between the approval of the biological innovator and the submission of a biosimilar registration application., implying that there is no link between the patent issue and the request for a biosimilar licence^[21].ANVISA has authorized a variety of biosimilars, notably rituximab, golimumab, certolizumab, abatacept, tocilizumab, infliximab, adalimumab and etanercept. Furthermore, in order to lower medicine costs and scarcity in the Brazilian market, 27 public and commercial laboratories formed a cooperation (known as Partnerships for Productive Development- PDP's) in 2013 to produce 14 biosimilars domestically.

Figure 3: Current Regulatory Acts Concerning Biological Products



Challenges for biologics in Brazil

- International non-proprietary name
- Interchangeability
- Extrapolation of indication

The FDA launched its final guidance on non-proprietary names for biological products, following a WHO proposal. Because the reference product and its biosimilars aren't exactly the same, they require distinct common names. This issue is resolved according to WHO and FDA, by using a hybrid term for biologicals that includes a core (which is the same for reference and biosimilars) and a four-letter suffix that is unique to every drug product.

ANVISA has not implemented the WHO naming suggestion or the FDA guidelines, and thus, there is no distinction between biosimilars and reference non-proprietary names in Brazil. This distinction is required to allow the medical practitioner to identify the medicine to be supplied and, probably more critically, to make sure the traceability required for safety evaluations.

Interchangeability refers to the ability to be switched or alternated during therapy without compromising on efficacy or safety. Interchangeability normally allows automatic substitution, which means the medical prescription can be substituted with an interchangeable product without involvement of a medical practitioner^[21].

Interchangeability in Brazil's point of view- The illustration of interchangeability is not compulsory for registering of the biosimilar product. Appropriate clinical studies must be carried out. ANVISA specifies that interchangeability is more closely associated with clinical practice rather than to regulatory status^{[21][33]}.It underlines the importance of medical assessment when it comes to biosimilar product substitution and interchangeability, as well as their references. As a result, the current law assigned this tough choice to customers or healthcare professionals^[21].

At present, ANVISA contemplates interchangeability only after the assessment of the clinical data acquired for this matter.

Extrapolation of therapeutic indications- According to ANVISA RDC 55/2010, It is necessary to adopt a sensitive test model capable of identifying possible variations between the biosimilar and comparator. The mode of action and/or the receptor(s) implicated should be same. It is also necessary to thoroughly characterise safety and immunogenicity.

ANVISA RDC 55/2010 covers extrapolation conditions that cannot be granted through an individual development pathway; however it doesn't resolve all of the difficulties that exist across different indications. Hence, more detailed regulation on this matter is required^[21].

Post-Registration Variations or Post-Approval Changes

RDC 49/2011 specifies the standards for biological product post registration variations, as well as other measures. DC 49/2011 classifies post-registration variations into three levels on basis of risk factor. They are as follows:

- Level 1 changes

- Level 2 changes
- Level 3 changes

Level 1 Changes (minor changes)

It doesn't need prior approval from ANVISA and can be instantly executed. These changes doesn't show any effect on product's quality.

Level 2 Changes (moderate changes)

Prior approval from ANVISA is essential for such changes. Changes that may have an effect on product quality, as well as non-compensatory techniques, are discussed in this level. A substantial amount of molecular analysis must be performed to show that the alteration has no impact on product quality.

Level 3 Changes (major changes)

Prior authorisation from ANVISA is needed. Changes that have a high likelihood of affecting the molecular structure and/or necessitating clinical studies are discussed which are referred to as: serious complication. This usually means that a new molecular characterization is required.

CONCLUSIONS

Brazil with an emerging market and population over 200 million is the major target and outlook for various Bio/Pharmaceutical companies around the globe. Even though it is one of the largest pharmaceutical markets, it has its challenges. For example, exporting of drugs to Brazil is a difficult task as it takes over couple of years for registration and further inhibition is that all communication should be done in their native language which is Portuguese.

ANVISA has brought many new resolutions which has increased the quality of registration of medicines in Brazil. As ANVISA has officially become ICH member, it is striving to meet ICH guidelines. ANVISA has introduced generic drug act in 1999 and comparability pathway for biosimilars in 2010; which has reduced the cost of medicines in Brazil. There are various challenges for biologics in Brazil which may include nomenclature, interchangeability, extrapolation indications.

In spite of having challenges, hindrance and on-uniformity in regulation and registration of drugs and biologics in Brazil, yet it is one of the largest pharmaceutical markets.

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Conflict of interests

Authors declare no conflict of interest amongst themselves.

Ethical approval

Since this work does not involve any animal studies it does not require Ethical approval.

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